IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 09/989,674
Applicant	: Gordon L. Woods
Filed	: November 21, 2001
TC/A.U.	: 1617
Examiner	: S. A. Jiang
Docket No.	: 2404-105
Customer No.	: 06449
Confirmation No.	: 1175

APPELLANT'S BRIEF

Mail Stop - Appeal Brief-Patents
Director of the United States Patent
and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

Applicant appeals from the Final Rejection of the claims of the above-referenced patent application dated December 31, 2002. The Commissioner is authorized to charge the fee required by 37 C.F.R. §1.17(c) and the fee required for a three month extension of time and additional fees to deposit account No. 02-2135. The current claims of this application are reproduced in Appendix A.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is CancEr2 Inc., incorporated in the state of Idaho.

II. RELATED APPEALS AND INTERFERENCES

Applicant is unaware of any appeals or interferences related to the subject matter of this appeal.

III. STATUS OF CLAIMS

Claims 20-25 and 61 are currently pending and are final rejection as a result of the Office Action mailed December 31, 2002. Claims 20-25 and 61 are appealed. Claims 1-19, 26-60, and 62-63 have been withdrawn as the result of a restriction requirement issued by the Patent Office.

IV. STATUS OF AMENDMENTS

An Amendment After Final was filed on June 20, 2003, concurrently with a Notice of Appeal, with proposed amendments to each of claims 20-25. None of the amendments were entered by the examiner. Appellant is submitting herewith an Amendment Pursuant to 37 C.F.R. 1.116, which presents again minor amendments to each of dependent claims 21, 23, 24 and 25 and cancels the claims that have been withdrawn as a result of the restriction requirement issued by the examiner. More specifically, the amendment to claim 21 corrects an error in the claim dependency; the amendments to the other claims cancel dependencies on a non-elected claim. These amendments have not yet been entered.

V. SUMMARY OF THE INVENTION

The present invention is directed to a method of regulating levels of cadmium in the body fluids and tissues of a human through the administration of one or more cadmium salts in an amount sufficient to balance the concentration of cadmium *per se* and to regulate the concentration of zinc relative to the concentration of cadmium in the person's body fluids and tissues (page 6, paragraph 0021). Cadmium has long been classified as a non-essential element and has been considered a toxin (page 9, paragraph 0031). Cadmium has been hypothesized in the literature to cause prostate cancer and hypertension in humans, based on apparent evidence of prostate cancer in men who had inhaled cadmium, evidence of high concentrations of cadmium in prostate cancer cells and cadmium-induced prostate cancer in rats. (*Id.)*

In contrast to these conventional beliefs, however, there is no evidence that ingested cadmium increases the incidence of prostate cancer (page 9, paragraph 0032). To the contrary, it has been found that the incidence of prostate cancer in countries in which the typical diet contains foods with relatively high amounts of cadmium have a low incidence of prostate cancer, whereas countries in which the typical diet is rich in foods containing relatively little cadmium have higher rates of prostate cancer (*Id.*). Furthermore, the Internationale Programme on Chemical Safety has stated that the evidence regarding cadmium as a cause of prostate cancer is inconclusive but does not support a conclusion of a causal relationship and that there is no convincing evidence that cadmium is an etiological agent of essential hypertension or of an increased mortality due to cardiovascular or cerebrovascular diseases (*Id.*). In

addition, although parenteral cadmium administration in rats has been shown to induce prostate cancer and hypertension in rats, several scientists have concluded that cadmium functions differently in rats than in humans; rat tissue is 30 times more sensitive to cadmium than is human tissue (page 10, paragraph 0034).

The present invention is based upon the premise that cadmium is, in contrast to conventional thought, an essential trace element (page 11, paragraph 0035). As defined in the application, an essential element is one which when administered, reverses a reduction in a biological function (*Id.*). The present application teaches that cadmium acts as a regulator of zinc (page 11, paragraph 0036). When the systemic levels of cadmium are out of balance (if there is a cadmium deficiency), the levels of zinc cannot be regulated properly (*Id.*). In a healthy person, the zinc:cadmium ratio is relatively high in cells and lower in fluids. Zinc is pumped into cells and cadmium is pumped out (*Id.*). If a person is cadmium deficient, however, cadmium does not get pumped out of the cell and, as a result, zinc is not pumped in (*Id.*). This, in turn, means that excess zinc in the fluids ultimately appears in the urine and is excreted. It is proposed that an underlying cause of certain diseases is a deficiency of cadmium leading to an increased urinary excretion of zinc and a secondary zinc deficiency (*Id.*).

It is believed that zinc and cadmium counterbalance one another in the body and that the movement of zinc and cadmium among red blood cells (erythrocytes), serum and cells provides an indication of relative health (page 12, paragraph 0037). The delivery of zinc from red blood cells to serum to cells of tissues is counterbalanced by the movement of cadmium from tissues to serum to red blood cells (*Id.*). A cadmium

deficiency results in a slowdown of the zinc delivery system from red blood cells to serum to cells (*Id.*).

When serum zinc decreases, urinary zinc excretion is decreased in a reflex fashion by a counter increased excretion of cadmium (page 12, paragraph 0038). If the body has an insufficient amount of cadmium, it is unable to counterbalance effectively urinary excretion of zinc, resulting in an increase in the amount of zinc excreted in the urine and a secondary zinc deficiency (*Id.*). It is theorized that a low cadmium diet causes a primary low level of cadmium in the body which is exaggerated by a high zinc diet which elevates the level of zinc in serum (*Id.*). When the elevated serum zinc level falls, it stimulates increased cadmium renal excretion which blocks excretion of renal zinc (*Id.*). This, in turn, results in a secondary cadmium deficiency, resulting in a cycle wherein a low cadmium diet causes a primary cadmium deficiency and a high zinc diet causes an increased urinary excretion of cadmium which causes a secondary cadmium deficiency (*Id.*). The cadmium deficiency then prevents the renal retention of zinc, and the increased urine excretion of zinc results in a secondary zinc deficiency (*Id.*).

It now has been found that a deficiency of cadmium in the human body hinders the movement of cadmium from cells of tissues to serum to red blood cells and, therefore, the counter-movement of zinc from red blood cells to serum to cells, leading to abnormal shifts in the levels of zinc and cadmium and, therefore, zinc-containing and prostaglandin E2 (PGE2)-dependent matrix metalloproteinases and that these fluctuations are associated with a number of diseases (page 14, paragraph 0041). For

example, it is known that zinc is a key component of proteases that function in cancer cell metastasis and that PGE2 increases cancer cell division (page 9, paragraph 0030).

Thus, in accordance with the teachings of this application, a person can be screened for an indication of or risk of developing a disease associated with unbalanced levels of cadmium in body fluids and tissues by measuring the level of cadmium in a sample of his or her body fluid to determine whether the level is outside of normal physiological levels (page 14, paragraph 0042). As defined in the application, "balancing" means to minimize or eliminate abnormal deviations in the level of cadmium in body fluids (page 17, paragraph 0049). Thus, to balance cadmium means to increase below-normal levels of, or abnormal shifts or fluctuations of, cadmium in body fluids to approximate normal physiological levels. (*Id.*).

In accordance with the present invention, a person's systemic cadmium levels can be balanced, and systemic levels of zinc accordingly can be regulated, through the administration of cadmium salts (page 18, paragraph 0059). The cadmium salts regulate the person's PGE2:PGF2α and zinc:cadmium ratios in the patient's blood, other body fluids and body fluid components and tissues by regulating the person's systemic levels of cadmium, zinc and PGE2. (*Id.*, and also page 20, paragraph 0054). In turn, as matrix metalloproteinases are regulated by zinc and PGE2, the systemic decrease in zinc and PGE2 levels resulting from the cadmium administration inhibits PGE2-dependent matrix metalloproteinases. By regulating the level of matrix metalloproteinases, zinc, and cadmium, the onset of diseases which have been shown to be associated with unregulated levels of zinc in body fluids and tissues and with

unregulated levels of matrix metalloproteinases in the body can be prevented or delayed, and the progression of such a disease in one who already has contracted it can be halted or slowed (*Id*).

Suitable cadmium salts that can be administered are bioavailable cadmium salts, including the sulfate, nitrate, chloride and acetate salts (page 21, paragraph 0059).

Independent claim 20 of this application is directed to a method of balancing the concentration of cadmium in body fluids and tissues of a human suffering from unbalanced levels of cadmium in his body fluids and tissues through the administration of a bioavailable and physiologically acceptable cadmium salt in a dosage regimen sufficient to balance said cadmium concentration. Support for this claim can be found on page 17, paragraph 0048 - page 18, paragraph 0051, and page 20, paragraph 0054 - page 21, paragraph 0059.

Dependent claim 21 provides that the unbalanced levels of cadmium are at least about 15% below normal; dependent claim 22 provides that the level is at least about 20% below normal. Support for these claims is found on page 15, paragraph 0045. Dependent claim 23 provides that the amount of cadmium salt administered in a series of daily doses at does levels of about 0.025 mg to about 2 mg per day. Support for this claim can be found on page 20, paragraph 0055. Dependent claim 24 provides that the cadmium salt is administered orally, parenterally or by inhalation. Support for this claim also is found on page 20, paragraph 0055. Dependent claim 25 identifies the cadmium salt as the sulfate, nitrate, chloride or acetate salt. Support for this claim can be found on page 21, paragraph 0059.

Independent claim 61 is directed to a method of correcting a cadmium deficiency in the body of a human suffering therefrom by administering to the human a bioavailable and physiologically acceptable cadmium salt in an amount sufficient to minimize or eliminate the deficiency. Support for this claim can be found on page 14, paragraph 0042, and page 15, paragraph 0045 - page 17, paragraph 0049.

VI. ISSUES

At issue in this appeal is whether the pending claims of this application are unpatentable under 35 U.S.C. §103(a) over the teachings of either Waalkes, M.P. et al., *J. Pharmacol. Exp. Ther.* 266(3): 1656-1563 (1993) (hereinafter referred to as Waalkes I), or Waalkes, M. P., *J. Pharmacol. Exp. Ther.* 277(2):1026-1033 (1996) (hereinafter referred to as Waalkes II). The examiner has asserted that both references disclose that cadmium is useful in pharmaceutical compositions and in the prevention or reduction of NDEA-induced tumor formation in the mouse liver or lung and that, in view of this teaching, one of ordinary skill in the art would have been motivated to use cadmium to balance the concentration of cadmium in a human's body fluids and tissues and to a correct a cadmium deficiency as there would have been a reasonable expectation that the administration of cadmium would have a beneficial therapeutic effect on balancing cadmium levels or correcting a cadmium deficiency in humans.

VII GROUPING OF THE CLAIMS

For purposes of this appeal, claims 20-25 and 61 stand together.

VIII ARGUMENT

Claims 20-25 and 61 are not obvious over either Waalkes I or Waalkes II.

Each of claims 20-25 is directed to a method of balancing the concentration of cadmium in body fluids and tissues of a human by administering to a human in need thereof a bioavailable and physiologically acceptable cadmium salt in a dosage regimen sufficient to balance said cadmium concentration. Claim 61 is directed to a method of treating a cadmium deficiency in the body of a human suffering therefrom by administering to the human a bioavailable and physiologically acceptable cadmium salt in an amount sufficient to minimize or eliminate the cadmium deficiency. Neither Waalkes I nor Waalkes II teaches or suggests that humans can suffer from unbalanced cadmium levels or a cadmium deficiency, much less that these conditions can be treated through the administration of a cadmium salt. Neither of the cited references makes any reference or suggestion regarding the administration of cadmium to humans; each references only discloses administering cadmium to mice.

The examiner's argument that the references render the claims obvious can be summarized as follows:

(a) both references disclose that cadmium is useful in pharmaceutical compositions and in the prevention or reduction of NDEA-induced tumor formation in the mouse liver or lung.

(b) these disclosures would motivate one of ordinary skill in the art to administer cadmium to balance the concentration of cadmium in a human's body fluids and tissues because one would have had a reasonable expectation that the administration of

cadmium would have a beneficial therapeutic effect on balancing cadmium concentrations in the body fluids and tissues of humans suffering from unbalanced levels of cadmium.

(c) mice are a good animal model for studying the effects of cadmium administration to humans because the references used mice and so one of skill in the art would acknowledge that mice are a good model for studying the effects of a pharmaceutical in humans.

(d) as cadmium is "known" to be an essential trace metal in humans, one of ordinary skill in the art would have recognized that administering cadmium in an amount below the toxic level to a human would have a reasonable expectation of success.

The examiner's argument is both circular and based on several unsubstantiated–and incorrect--premises, as discussed below, and fails to establish a *prima facie* case of obviousness.

1. Prior to the Appellant's invention, it was not recognized in the art that humans can suffer from a cadmium deficiency or imbalance.

As Appellant has explained in his application, cadmium has long been viewed as a toxic, non-essential metal with respect to humans. This is illustrated by statements in the very references upon which the examiner relies. Waalkes I states that cadmium is "a non-essential, toxic transition metal" that is a "suspected human carcinogen" and a "highly cytotoxic agent" (page 1656), and Waalkes II notes that cadmium is a "toxic,

nonessential transition metal that is classified as a human carcinogen and is a potent animal carcinogen" (page 1026).

A review of the art finds numerous references published over the last 15 years which echo these statements. Appellant submitted to the examiner a large number of abstracts of scientific papers, obtained through a Medline database search, which state directly, time and again, that cadmium is a toxic and non-essential metal. For example, the abstract for Suzuki, K.T., et al. *Toxicol. Appl. Pharmacol.* 105(3):413-421 (1990), refers to cadmium as a "nonessential heavy metal," as does the abstract for Ellen, G., et al. *Food Addit Contam* 7(2):207-221 (1990). The abstract of Berner, Y.N., et al., *Am. J. Clin. Nutr.* 50(5):1079-83 (1989) describes cadmium as a "toxic" ultratrace element. The abstract of Brandle, J.E. et al., *Genome* 36(2):255-260 (1993) states that "[c]admium (Cd) is a nonessential heavy metal that can cause acute and chronic illness in humans." The abstract for Elsenhans, B., et al., *Hum. Exp. Toxicol.* 16(8):429-434 (1997) refers to cadmium as a nonessential, toxic metal. The abstract of Krachler, M., et al. *Eur. J. Clin. Nutr.* 53(6):486-494 (1999) also identifies cadmium as a non-essential and toxic element.

Furthermore, a 1999, 400 page, *Toxicological Profile for Cadmium* prepared for the U.S. Department of Health and Human Services states bluntly that "[t]here are no known good effects from taking in cadmium" (page 5, also submitted to the examiner with the Amendment After Final).

Appellant also provided to the examiner two papers published in 1996, in which USDA scientists assessed the question of whether a number of "ultratrace" elements

could be considered essential elements. The paper by Uthus and Seaborn provides that twelve such elements, including cadmium, "have not been shown to be essential for humans" but that apparent deficiency signs and beneficial effects have been found in animal studies. They assert that of these twelve elements, only arsenic, nickel, silicon and vanadium have the most compelling circumstantial evidence for essentiality, and they discuss only those elements in detail. For the other elements, they note at the end of their paper that "[t]he data for the remaining ultratrace elements (aluminum, bromine, *cadmium*, germanium, lead, lithium, rubidium and tin) *are so limited and controversial that listing dietary concentrations that elicit beneficial effects is not warranted at this time. ... [D]ata are so limited for these ultratrace elements that we feel using extrapolated animal data is inappropriate*" (page 2457S; emphasis added). Similarly, the paper by Nielsen argues that among the ultratrace elements, six, such as iodine and selenium, merit specific recommended daily allowances (RDAs), another six, such as fluoride and nickel, could be identified as meriting "apparent beneficial intake" (ABI) based on extrapolation of data from animals to humans, but that the "*evidence is too limited or controversial for the remaining ultratrace elements [including cadmium] to even provide an ambiguous ABI*" (see abstract). Thus, scientists looking specifically to make recommendations on the intake of cadmium in 1996 (i.e., three years after the publication of Waalkes I and contemporaneously with the publication of Waalkes II) were unwilling to suggest that the administration of cadmium to humans could be beneficial.

In view of all of these references, Applicant submits that it is clear that at the time of his invention it was not recognized or accepted in the art that humans can suffer from a deficiency or imbalance of cadmium and that such a deficiency or imbalance could or should be corrected through the administration of cadmium.

2. The examiner's assertion that Appellant has "admitted" that cadmium is an essential trace metal in human is incorrect.

In the final Office Action, the examiner asserted that Appellant had "admitted" that cadmium is an essential trace element in humans, thereby implying that the essentiality of cadmium had been known in the art prior to the Appellant's invention. To the contrary, as the discussion in the application and the references Appellant has submitted to the examiner clearly show, it was not known in the art that cadmium in an essential trace metal in humans. It is the Appellant's determination of the essentiality of cadmium, despite the accumulation of published reports to the contrary, that provides the basis for his invention. The premise underlying the present invention is that it is an imbalance or deficiency, rather than the mere presence, of cadmium in the human body that actually is associated with the onset or increased severity of certain diseases or disorders. Specifically, it appears that an underlying cause of certain health problems is a deficiency of cadmium which, in turn, leads to an increased urinary excretion of zinc and a secondary zinc deficiency. If cadmium levels in body fluids and tissues are out of balance, zinc levels also will be out of balance. Through cadmium administration,

levels of cadmium and zinc in body fluids and tissues can be brought into balance and a cadmium deficiency can be minimized or eliminated.

3. Neither Waalkes reference makes any reference to human treatment or suggests the administration of cadmium to humans

Both Waalkes I and Waalkes II report only the results of initial animal studies in which cadmium was administered to mice with induced liver and lung tumors. One of ordinary skill in the art could not draw any conclusions from these papers as to the ultimate role of cadmium as a therapeutic agent for humans. Indeed, the Waalkes I paper acknowledged that very point. At the conclusion of this paper, the authors stated only that "[t]he potential chemotherapeutic effects of cadmium deserve further study." This statement was echoed in the Waalkes II paper: "the potential chemotherapeutic effects of cadmium deserve additional study." As the authors do not set forth any conclusions with regard to their studies in mice, certainly no conclusions can be drawn by others regarding the administration of cadmium to humans, especially in view of the long-held assessment within the scientific community that cadmium is a non-essential, toxic metal.

These references do no more than raise the possibility that cadmium, on the basis of studies conducted in mice, under certain circumstances, may act as a therapeutic agent, specifically as an anti-neoplastic agent. This is far removed from rendering it obvious that humans can suffer from a deficiency or an imbalance of

cadmium in their body fluids and tissues which can be corrected through the administration of a cadmium salt.

4. There is no evidence in the record that mice are a good model for humans with regard to the administration of cadmium

Although the examiner has asserted that the mouse is a good model for studying the effects of cadmium administration to humans, she has based that conclusion simply on the fact that Waalkes administered cadmium to mice. This does not provide a sufficient foundation for the examiner's conclusion. There is no evidence in the record that mice are, in fact, a good animal model for humans with respect to the administration of this particular agent. The fact that an initial study was carried out using a particular animal species does not establish that that animal species *necessarily* is a good model for humans. Neither Waalkes I nor Waalkes II make any statement that mice are good models for humans with regard to the administration of cadmium for any purpose, nor is there any indication in the papers that mice can suffer from a systemic cadmium imbalance or deficiency. Neither of the papers provides any information on the systemic levels of cadmium of the mice at the beginning of or during the studies, much less whether those levels were typical or atypical murine cadmium levels.

5. In view of the foregoing deficiencies, the examiner has failed to establish a *prima facie* case of obviousness

A prima facie case of obviousness is established only if the following criteria are met:

(1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process

and

(2) the art also must have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the application. *In re Vaeck* 20 USPQ2d 1438 (F.Cir. 1991). Here, neither of the two criteria are met. The cited art does not teach or suggest that mice, much less humans, can suffer from a cadmium deficiency. The references do not suggest administering cadmium to humans for any purpose, much less to treat a cadmium deficiency or imbalance. As the problem was not recognized, and the treatment was not suggested, the references certainly do not provide a reasonable expectation that the administration of cadmium to humans would be beneficial. To conclude otherwise is to rely upon hindsight gleaned from the teachings of the present application, and a determination of obviousness cannot be predicated upon hindsight. *Gore v. Garlock*, 220 USPQ 303 (F.Cir. 1983). The pending claims are not obvious in view of the cited references.

Conclusion

In view of the foregoing arguments, the rejection of the pending claims under 35 U.S.C. §103 in view of Waalkes I or Waalkes II should be reversed.

☒ Customer Number or Bar Code Label **6449**					
Name	Barbara G. Ernst, Reg. No. 30,377				
Signature	Barbara G. Ernst			*Date*	Nov. 20, 2003
Address	Rothwell, Figg, Ernst & Manbeck Suite 701-East, 555 13th Street, N.W.				
City	Washington	*State*	D.C.	*Zip Code*	20004
Country	U.S.A.	*Telephone*	202-783-6040	*Fax*	202-783-6031

Claims on Appeal

20. A method of balancing the concentration of cadmium in body fluids and tissues of a human which comprises administering to a human suffering from unbalanced levels of cadmium in his body fluids and tissues a bioavailable and physiologically acceptable cadmium salt in a dosage regimen sufficient to balance said cadmium concentration.

21. The method of claim 20, wherein said unbalanced levels of cadmium are at least about 15% below normal.

22. The method of claim 20, wherein said unbalanced levels of cadmium are at least about 20% below normal.

23. A method in accordance with claim 20, wherein said cadmium salt is administered in a series of daily doses at dose levels of about 0.025 mg to about 2 mg per day.

24. A method in accordance with claim 20, wherein said cadmium salt is administered orally, parenterally or by inhalation.

25. The method of claim 20, wherein said cadmium salt comprises the sulfate, nitrate, chloride or acetate cadmium salt.

61. A method for correcting a cadmium deficiency in the body of a human suffering therefrom which comprises administering to said human a bioavailable and physiologically acceptable cadmium salt in an amount sufficient to minimize or eliminate said cadmium deficiency.